

REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1-97 are pending.

The claim amendments are supported by the original disclosure and, thus, no new matter has been added. Entry of the amendments is requested because it was improper for the rejections to be made final in the previous Office Action.

1. Finality is improper and should be withdrawn.

Applicants respectfully submit that the final rejections made in the Office Action (Paper No. 24) mailed November 21, 2002 are improper and should be withdrawn. More specifically, the Office Action contains "new grounds of rejection" that were not necessitated by amendment. Therefore, the finality of the office action is improper and should be withdrawn.

Claims 1-14 and 15-40 were not amended in Applicants' response filed October 11, 2002. The Examiner then issued new grounds of rejection under 35 U.S.C. 112, first paragraph, and under 35 U.S.C. 103 (relying on the newly cited reference by Merrick et al.) in the next Office Action (Paper No. 24). Applicants had no previous opportunity to review and respond to these new rejections. As stated in the M.P.E.P.,

Before final rejection is in order a clear issue should be developed between the examiner and applicant . . . the goal of reaching a clearly defined issue for an early termination, i.e., either an allowance of the application **or a final rejection** . . . While the rules no longer give to an applicant the right to "amend as often as the examiner presents new references or reasons for rejection," **present practice does not sanction hasty and ill-considered final rejections.** The applicant who is seeking to define his or her invention in the claims that will give him or her the patent protection to which he or she is justly entitled should receive the cooperation of the examiner to that end, and not be prematurely cut off in the prosecution of his or her application . . . The examiner should never lose sight of the fact that in every case the applicant is entitled to a full and fair hearing, and **that a clear issue between applicant and examiner should be developed**, if possible, before appeal.

[M.P.E.P. § 706.07, emphasis added].

Since the Office Action contains new grounds of rejection not necessitated by amendment, the final rejections are improper. Applicants respectfully submit that under such circumstances, they are unable to develop a “clear issue” and understanding with the Examiner. Since the new grounds of rejection (and a newly cited reference) were not of record in the Office Action (Paper No. 22) mailed July 30, 2002, it is respectfully submitted that the next Office Action (Paper No. 24) should not have been made final and Applicants request that the finality of the Office Action be withdrawn.

2. Claim rejections under the first and second paragraphs of 35 U.S.C. 112 are improper and should be withdrawn.

Claims 1-61 are rejected under the “written description” requirement of 35 U.S.C. § 112, first paragraph, as allegedly not supported in the specification and claims 1-40 remain rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The Examiner alleges “a complete recitation of the section under discussion indicated that support for the terminology not in the specification as filed – involving a departure from the application as filed will result in a rejection under section 112” (Paper No. 24, page 2).

Applicants respectfully traverse the rejection under Section 112, first paragraph. It is unclear how the Examiner arrives to her conclusions. The present claims are fully supported by the specification as originally filed in compliance with the requirements of Section 112, first paragraph. A person of skill in the art would recognize that the indicated limitation is supported by the original disclosure.

Applicants submit that the subject matter of the claim need not be described literally (i.e., using the same terms or in haec verba) in order for the disclosure to satisfy the description requirement of Section 112, first paragraph (M.P.E.P. § 2163.02). One of skill in the art would readily recognize that the Applicants had possession of the claimed invention at the time of filing the application. Absent a requirement for literal support, the inherent support in the specification is sufficient to satisfy the requirements of Section 112, first paragraph.

More specifically, persons of ordinary skill in the art, such as Merrick et al. (the reference cited by the Examiner), clearly recognized that “Total DNA as a contaminant in bio-pharmaceutical products is of concern because of its potential risk” (Merrick et al., page 399). A person of skill in the art also would recognize that a threshold value for the total DNA contamination of the sample which divides the acceptable and unacceptable levels is established by a regulatory body, such as WHO, and that the instant invention is concerned with improved methods for reliably measuring the DNA levels with respect to acceptable and unacceptable amounts. The present invention is specifically directed to assay methods for measuring the amount of nucleic acid in a sample. The specification explicitly teaches:

The development of therapeutic biopharmaceuticals for human injection generated through recombinant deoxyribonucleic acid (DNA) technology has resulted in new standards for product purity. Viral contamination of several vaccines initially demonstrated the safety risk associated with the products generated from recombinant technology. Thus, contamination of products by host cell DNA could be a biological hazard for the recipient. The primary concern of regulatory agencies is the potential contamination of product with oncogenes or infectious viral DNA. . . . Because the risk associated with exposure of 100 pg of DNA per dose is negligible, **the WHO (World Health Organization) currently requires the DNA in all biopharmaceuticals to be below 100 pg per dose. Thus, methodologies that accurately determine picogram amounts of DNA have become a requisite in the bio-pharmaceutical field.**

[Specification, page 1, lines 7-19, emphasis added].

The assay methodologies are at least implicitly described as being capable of accurately determining picogram amounts of DNA as per the above-described requisite in the biopharmaceutical field. The specification also describes certain prior art methods as having “limitations with respect to the ability to detect low picogram amounts of DNA” (Specification, page 2, lines 14-16). One of skill in the art would readily recognize that Applicants were in possession of the claimed methods at the time of filing of this application, including the limitation “determining whether the total nucleic acid in said sample is higher or lower than . . . 100 pg”.

Finally, Applicants remind the Examiner that the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that,

as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563-64, 19 USPQ2d at 1117. Applicants urge that a person of ordinary skill in the art would recognize from the disclosure in the specification that Applicants were in possession of the instant invention at the time the application was filed. Namely, Applicants were in possession of assay methods for measuring total nucleic acid in the sample and determining whether the sample met the 100 pg threshold level established by the WHO. Indeed, Example 5 of the present specification demonstrates the successful detection of 5 pg of contaminating DNA in the sample, which is 20-fold lower than the WHO threshold level (see also Examples 2 and 9).

The Examiner further alleges “the threshold limitation, even when considered in view of the WHO information does not indicate that volume from in which the 100 pg is considered as a threshold. Simply 100 pg in a liter is clearly distinct from a deciliter.” (Paper No. 24, page 4).

Applicants submit that the limitation objected to by the Examiner under Section 112, second paragraph, is clear and definite to one of ordinary skill.

Applicants direct the Examiner’s attention to the disclosure in Merrick et al. that “Hybridization can detect less than 10 pg of specific DNA [. . .], 2 pg of DNA can be detected in a nonradioactive format [. . .]” (Merrick et al., page 399).

The art routinely defines contamination amounts as total amounts and not concentrations (see Merrick et al.). Such definitions are easily understood by a skilled artisan. Furthermore, this is the only practical way to define harmful contamination. When the medication is delivered in a specific volume, or a pill, the concentration of the contaminant does not matter; the total amount delivered by the medication does matter. For example, a single 1 ml injection of a biopharmaceutical containing 100 pg of total DNA is as unacceptable as a single one liter injection of a drug containing 100 pg of contaminating DNA.

Therefore, Applicants urge that this rejection is improper and should be withdrawn.

With respect to the rejection of claims 1-14 and 16-40 under Section 112, second paragraph, a claim cannot be rejected solely because of the language used to define the subject matter for which patent protection is sought. *In re Swinehart*, 160 USPQ 226 (CCPA 1971). The focus in determining compliance with the requirement of Section 112, second paragraph, should be whether the claims meet the threshold requirements of clarity and precision, not whether more suitable language or modes of expression are available (M.P.E.P. § 2173.02).

Applicants urge the claims are sufficiently clear and definite to one of ordinary skill in the art when properly construed in view of the specification and what is known in the art (M.P.E.P. § 2173). One of ordinary skill in the art would readily understand the meaning of the terms “a threshold amount of contamination” and “the threshold amount of contamination is equal to or less than 100 pg” as recited in the present claims (see, for example, Claim 1) when properly construed in view of the specification. One of ordinary skill in the art would understand that the methods distinguish samples having a level of contamination below the threshold amount from samples having levels of contamination above the threshold. It would also be understood that the assay must be sufficiently sensitive so that this threshold value can be set at 100 pg (e.g., the WHO requirement) or less (e.g., the 5 pg detection limit from Example 5). One of ordinary skill in the art would be familiar with such terminology and familiar with defining assay sensitivity in the terms of total detectable amount of analyte (e.g. 100 pg) independently of the sample volume. The M.P.E.P. clearly states:

[The Examiner] should allow claims which define the patentable subject matter with a reasonable degree of particularity and distinctness. Some latitude in the manner of expression and the aptness of terms should be permitted even though the claim language is not as precise as the examiner might desire.

In reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph. See, e.g., *Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000). See also *In re Larsen*, No. 01-1092 (Fed. Cir. May 9, 2001) (unpublished)

[M.P.E.P. § 2173.02].

Applicants maintain that the rejections are improper for the reasons set forth above. Accordingly, Applicants urge that the rejections under Section 112, first and second paragraphs, should be withdrawn.

3. Claim 58 is rejected under 35 U.S.C. 112, first paragraph, as allegedly unclear.

Claim 58 is intrinsically supported by the disclosure in the specification. The working examples of the present specification describe the detection of total DNA from different sources: calf thymus (Examples 9-11) and *S. cerevisiae*, mouse and *E. coli* (Example 11). A person of skill in the art will readily recognize that total DNA extracts from four different species are highly unlikely to contain only a single DNA molecule.

Therefore, claim 58 is supported by the original disclosure and its rejection under 35 U.S.C. 112, first paragraph, is improper and should be withdrawn.

4. The present claims are not obvious over cited prior art.

Claims 1-3, 6-12, 14-25, 28-32 and 34-37 were rejected under 35 U.S.C. § 103 as allegedly obvious over Hartley (U.S. Patent No. 5,043,272) in view of Eberle (U.S. Patent No. 5,413,906) and Merrick et al. (Biotech Forum Europe 9:398-403, 1992) ("Merrick" hereinafter). Claims 4-5, 13, 26-27, 33 and 39-40 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over Hartley in view of Merrick, Wu et al. (Genomics 4:560-569, 1989), and Respass (U.S. Patent No. 5,599,662). Claim 38 was rejected under 35 USC § 103(a) as allegedly obvious over Hartley in view of Kozlowski et al. (U.S. Patent No. 6,096,499) and Merrick. These rejections will be addressed collectively.

Applicants respectfully traverse these rejections. As admitted by the Examiner, the method for measuring total nucleic acid in the sample would not have been obvious to the person having ordinary skill in the art from the disclosure of Hartley since column 8, lines 39-43, merely teaches a kit which "will contain in addition to the reagents listed above, a probe for detecting the papilloma virus" (Hartley, col. 8, lines 45-46). Nothing in the disclosure of Hartley teaches or suggests that this probe can be used for the quantification of **the total amount** of the nucleic acid contamination in the sample. Instead,

Hartley is clearly directed to measuring the amount of a specific nucleic acid, not total nucleic acid.

Claims 1-3, 6-12, 14-25 and 34-37 relate to a method for measuring **total** nucleic acid in the sample. The fact that low starting levels of specific DNA (HPV 18 and HPV 16), such as 100 pg, may be amplified by the method of Hartley does not teach or suggest the claimed invention and therefore is not sufficient for a Section 103 rejection. A method that is shown to amplify low levels of the specific DNA in a sample cannot be considered a good predictor for the success in the amplification of the **total** contaminating DNA molecules. Hartley fails to teach or suggest how the amount of total DNA in the sample can be measured at the detection threshold of the instant invention, e.g., 100 pg.

Furthermore, Applicants maintain that the disclosure of Hartley misses essential elements of the pending claims and therefore does not teach or suggest every element of the currently pending claims, and does not teach or suggest the present invention as a whole. Hartley suggests derivatizing primers with biotin or attaching oligonucleotides to the capture beads exclusively to improve the detection of the specific nucleotide sequences (e.g., HPV 16 DNA was detected using capture beads in Table II). Hartley does not teach or suggest how to use biotin-derivatized primers or capture beads to measure the amount of **total** nucleic acid in the sample. Therefore, Hartley does not teach or suggest the presently claimed invention.

Applicants submit that Eberle does not compensate for the deficiencies of Hartley. In fact, Eberle teaches away from the present invention. Unlike measuring the total nucleic acid in the sample in a sequence independent manner, Eberle discloses a highly selective detection method:

The method is highly specific since only immobilized nucleotides and nucleic acids containing the latter are bound to the solid phase. Samples with a less-than-maximum degree of purity are, hence, also acceptable for the method of the invention. Even determination in the presence of bacteria is, for example, possible.

[Eberle, column 7, lines 3-9].

Contrary to the instant invention which is directed to measuring the amount of total contaminating DNA, the invention of Eberle teaches detection of highly specific sequences of interest with no sensitivity for contaminating nucleic acids. As specifically stated in the citation above, the bacterial DNA would not be amplified by the method of Eberle.

Therefore, neither the teachings of Eberle nor the teachings of Hartley teach or suggest measuring total nucleic acid concentration in a sample with a mixed starting material. One of ordinary skill in the art would not have been motivated to modify the teachings of Hartley in view of the teachings of Eberle to result in the presently claimed invention.

Merrick also fails to compensate for the deficiencies of Hartley. Although Merrick teaches the detection of total DNA in a sample, the system of Merrick, when combined with the amplification of Hartley or Eberle, does not result in a present invention. The disadvantages of the threshold system of Merrick are described in the specification (Specification, page 2) which clearly states:

Disadvantages to the total DNA assay performed on a threshold system (Molecular Devices) include the narrow dynamic range, the technically challenging and time consuming protocol. In addition, the inability to accurately detect fragments of DNA below 872 basepairs severely limit the overall sensitivity of the assay. In fact, decreasing the size of DNA below 872 basepairs inhibits the detection of fragments greater than 872 basepairs. The lack of sensitivity for smaller DNA fragments is a major disadvantage of this methodology because the significant quantity of DNA in protein therapeutic samples is fragmented.

[Specification, page 2].

Thus, one of ordinary skill in the art would not have been motivated to modify the teachings of Hartley, alone or in combination with Eberle, in view of the teachings of Merrick to result in the presently claimed invention.

Moreover, there would have been no motivation to combine the teachings of Hartley with those of Merrick since the teachings are not combinable. The 800 basepair HPV type 18 DNA sequence of Hartley (col. 9, lines 65-66) **cannot** be detected with the system of Merrick due to the 872 basepair limitation on that system described in the present specification. If the modification proposed in the Office Action would render the

prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984) (see also M.P.E.P. § 2143.01).

Applicants further urge that there is no suggestion or motivation to combine the teachings of Hartley et al with the teachings of Eberle and Merrick. Therefore, the Examiner fails to provide the required factual support to establish a prima facie case of obviousness. **The suggestion to combine the elements must come from a reference cited and not from the applicant's disclosure.** See *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988) (emphasis added). Hartley and Eberle do not teach or suggest detecting the amount of total DNA in the sample. Merrick does not teach or suggest the desirability of combining the threshold detection system with amplification protocols of Hartley and Eberle. In fact, the system of Merrick will not work with the fragment of Hartley for the reasons set forth above, while the system of Eberle is highly specific for a selected DNA and would not improve the total DNA detection of Merrick. To establish a case of prima facie obviousness based on combination of references, the Examiner is required to demonstrate that the prior art provide "a reason, suggestion, or motivation to lead an inventor to combine those references." *Pro-Mold and Tool Co. v. Great Lakes Plastics Inc.*, 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996).

[E]vidence of a suggestion, teaching, or motivation to combine may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or in some cases, from nature of the problem solved. . . .

The range of sources available, however, **does not diminish the requirements for actual evidence. That is, the showing must be clear and particular.**

In re Dembiczak, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) (citation omitted, emphasis added).

Similarly, there is no suggestion or motivation to combine Hartley with Merrick, Wu et al., Respass and/or Kozlowski et al. The combined references fail to compensate for the deficiencies of Hartley.

Wu et al. merely teaches sequence specific nucleic acid amplification. It does not teach or suggest that a sensitivity level of 100 pg is achievable with the method of Wu et

al. The reference also does not teach or suggest the amplification of the total contaminating DNA in a sample. On the contrary, the reference specifically states:

We have previously demonstrated that a single base pair mismatch between the template and the substrate oligonucleotides reduces the efficiency of ligating the octamer and tetradecamer substrate pairs. When a hexamer is used instead of the octamer as the 3' substrate, enzyme discrimination of the matched and mismatched base pair is even more pronounced.

[Wu et al., page 563].

Applicants maintain that a person of ordinary skill in the art would not have a reasonable expectation of success in amplifying the total contaminating DNA in the sample based on the disclosure of Wu et al. Therefore, by teaching the strong dependence of the amplification efficiency on the exact primer – template match, Wu et al. effectively teaches away from the present invention. Furthermore, the Hartley and Merrick references can not be combined for the reasons set forth above. Absent a suggestion or teaching to make a combination suggested by the Examiner in the cited references, the rejection is improper and should be withdrawn.

Respass also does not teach or suggest the currently pending subject matter and therefore does not compensate for the deficiencies of Hartley, Merrick and Wu. Hartley and Merrick can not be combined for the reasons set forth above. Respass merely provides sequences of improved primers for the PCR amplification of one highly specific nucleic acid sequence of a pol gene from HIV-1. The reference does not teach or suggest amplifying total contaminating DNA in the sample. Neither does the reference teach or suggest the sensitivity limit for a quantitative detection of the contaminating DNA on the order of 100 pg. Finally, absent a suggestion or teaching to make the combination proposed by the Examiner in the cited references, the rejection is improper and should be withdrawn.

Kozlowski et al. does not compensate for the deficiencies of Hartley and Merrick. Absent a suggestion or teaching to make the combination proposed by the Examiner in the cited references, the rejection is improper and should be withdrawn. Hartley and Merrick cannot be combined for the reasons set forth above. Furthermore, Kozlowski et al. merely teach screening for modulators of the primase activity and do not teach the

amplification of total contaminating DNA in the sample with a sensitivity on the order of 100 pg.

Applicants maintain that Hartley (U.S. Patent No. 5,043,272) alone or in combination with Eberle (U.S. Patent No. 5, 413, 906), Merrick et al. (Biotech Forum Europe 9:398-403, 1992), Wu et al. (Genomics 4:560-569, 1989), Respass (U.S. Patent No. 5,599,662) and Kozlowski et al. (U.S. Patent No. 6,096,499) fail to teach or suggest the presently claimed subject matter. Withdrawal of the Section 103 rejection of claims 1-3, 6-12, 14-25, 28-32 and 34-38 is respectfully requested.

5. Claims 41-57 and 59-61 are not obvious over Hartley.

Claims 41-57 and 59-61 were rejected under 35 U.S.C. § 103 (a) as allegedly obvious over Hartley (U.S. Patent No. 5,043,272).

The Examiner admits that "Hartley does not disclose that the method is for determining the amount of total nucleic acid contamination in the sample as recited in the preamble of claims 41-45" (Paper No. 24, page 11). But she alleges, "It would have been prima facie obvious to carry out the method as claimed." *Id.*

Applicants respectfully traverse. The method for measuring total nucleic acid in the sample would not have been obvious to a person having ordinary skill in the art from the disclosure of Hartley since column 8, lines 39-43, merely teaches a kit which "will contain in addition to the reagents listed above, **a probe for detecting the papilloma virus**" (Hartley, col. 8, lines 45-46, emphasis added).

Hartley specifically identifies a probe as specific for a papilloma virus. Nothing in the disclosure of Hartley teaches or suggests that this probe can be used for the quantification of **the total amount** of the nucleic acid contamination in the sample. Instead, Hartley is clearly directed to measuring the amount of a specific nucleic acid, not total nucleic acid. It is improper to rely on speculative assumptions regarding the meaning of a claim and then base a rejection under 35 U.S.C. § 103 on these assumptions. *In re Steele*, 305 F.2d 859, 134 U.S.P.Q. 292 (CCPA 1962).

Therefore, the rejection is improper and should be withdrawn.

6. Claim 58 is not obvious Hartley and Caskey et al.

Hartley does not disclose the present invention for the reasons set forth above and in view of the Examiners admission: "Hartley does not disclose that the method is for determining the amount of total nucleic acid contamination in the sample as recited in the preamble of claims 41-45" (Paper No. 24, page 11).

Caskey et al. (U.S. Patent No. 5,364,759) do not compensate for the deficiencies of Hartley. Caskey et al. merely teach a multiplex polymerase chain reaction in which two or more different, but **specific** sequences are amplified. Caskey et al. do not teach or suggest amplifying "total amount of nucleic acid contamination [which] comprises two or more different nucleic acid species of **unknown sequence**" (see Claim 58, emphasis added).

Applicants submit that none of the references, alone or in combination, teach or suggest the instant invention as a whole. Applicants respectfully submit that the Examiner does not provide the required factual support to establish a prima facie case of obviousness. The M.P.E.P. clearly states:

To establish *prima facie* obviousness of a claimed invention, **all the claim limitations must be taught or suggested by the prior art.** *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

[See M.P.E.P. § 2143.03, emphasis added].

Hartley alone or in combination with Caskey et al. does not teach or suggest detecting a total amount of nucleic acid contamination which comprises two or more different nucleic acid species of unknown sequence and therefore do not teach or suggest the presently claimed subject matter. The withdraw of the claim 58 rejection under 35 USC 103(a) is earnestly solicited.

Conclusion

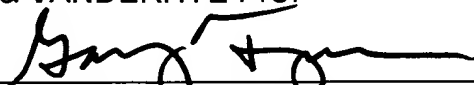
In view of the comments herein, the present application is believed to be in condition for allowance or in better condition for an appeal. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited.

Moreover, Applicants believe that an interview would be helpful in addressing any issue which is not successfully traversed in or overcome by this response. Thus, Applicants respectfully request an interview with the Examiner once this response has been reviewed.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____


Gary R. Tanigawa
Reg. No. 43,180

1100 North Glebe Road, 8th Floor
Arlington, VA 22201-4714
Telephone: (703) 816-4000
Facsimile: (703) 816-4100

APPENDIX
MARKED-UP VERSION TO SHOW CHANGES

IN THE CLAIMS

Claims 62-97 are added as new claims.

1